Answer 1:

Bibliographic Information

Multidrug Resistance-Associated Protein-Overexpressing Teniposide-Resistant Human Lymphomas Undergo Apoptosis by a Tubulin-Binding Agent. Aneja, Ritu; Liu, Min; Yates, Clayton; Gao, Jinmin; Dong, Xin; Zhou, Binfei; Vangapandu, Surya N.; Zhou, Jun; Joshi, Harish C. Department of Cell Biology, Emory University School of Medicine, Atlanta, GA, USA. Cancer Research (2008), 68(5), 1495-1503. Publisher: American Association for Cancer Research, CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 148:393897 AN 2008:272396 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Several DNA- and microtubule-binding agents are used to manage hematol. malignancies in the clinic. However, drug resistance has been a challenge, perhaps due to a few surviving cancer stem cells. Toxicity is another major impediment to successful chemotherapy, leading to an impoverished quality of life. Here, we show that a semisynthetic nontoxic tubulin-binding agent, 9-bromonoscapine (EM011), effectively inhibits growth and regresses multidrug resistance-assocd. protein (MRP)-overexpressing teniposide-resistant T-cell lymphoma xenografts and prolongs longevity. As expected, teniposide treatment failed to regress teniposide-resistant xenografts, rather, treated mice suffered tremendous body wt. loss. Mechanistically, EM011 displays significant antiproliferative activity, perturbs cell cycle progression by arresting mitosis, and induces apoptosis in teniposide-resistant lymphoblastoid T cells both in vitro and in vivo. EM011-induced apoptosis has a mitochondrially-mediated component, which was attenuated by pretreatment with cyclosporin A. We also obsd. alterations of apoptosis-regulatory mols. such as inactivation of Bcl2, translocation of BAX to the mitochondrial membrane, cytochrome c release, and activation of downstream apoptotic signaling. EM011 caused DNA degrdn. as evident by terminal deoxynucleotidyl transferase-mediated dUTP-biotin end labeling staining of the increased concn. of 3'-DNA ends. Furthermore, the apoptotic induction was caspase dependent as shown by cleavage of the caspase substrate, poly(ADP)ribose polymerase. In addn., EM011 treatment caused a suppression of natural survival pathways such as the phosphatidylinositol-3'-kinase/Akt signaling. These preclin. findings suggest that EM011 is an excellent candidate for clin. evaluation.

Answer 2:

Bibliographic Information

The synthesis, discovery, and development of a highly promising class of microtubule stabilization agents: curative effects of desoxyepothilones B and F against human tumor xenografts in nude mice. Chou, Ting-Chao; O'Connor, Owen A.; Tong, William P.; Guan, Yongbiao; Zhang, Zui-Guo; Stachel, Shawn J.; Lee, Chulbom; Danishefsky, Samuel J. Preclinical Pharmacology Core Facility, Memorial Sloan-Kettering Cancer Center, New York, NY, USA. Proceedings of the National Academy of Sciences of the United States of America (2001), 98(14), 8113-8118. Publisher: National Academy of Sciences, CODEN: PNASA6 ISSN: 0027-8424. Journal written in English. CAN 135:327022 AN 2001:526491 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

We have evaluated two synthetic epothilone analogs lacking the 12,13-epoxide functionality, 12,13-desoxyepothilone B (dEpoB), and 12,13-desoxyepothilone F (dEpoF). The concns. required for 50% growth inhibition (IC50) for a variety of anticancer agents were measured in CCRF-CEM/VBL1000 cells (2,048-fold resistance to vinblastine). By using dEpoB, dEpoF, aza-EpoB, and paclitaxel, the IC50 values were 0.029, 0.092, 2.99, and 5.17 μM, resp. These values represent 4-, 33.5-, 1,423- and 3,133-fold resistance, resp., when compared with the corresponding IC50 in the parent [nonmultiple drug-resistant (MDR)] CCRF-CEM cells. We then produced MDR human lung carcinoma A549 cells by continuous exposure of the tumor cells to sublethal concns. of dEpoB (1.8 yr), vinblastine (1.2 yr), and paclitaxel (1.8 yr). This continued exposure led to the development of 2.1-, 4,848-, and 2,553-fold resistance to each drug, resp. The therapeutic effect of dEpoB and paclitaxel was also compared in vivo in a mouse model by using various tumor xenografts. DEpoB is much more effective in reducing tumor sizes in all MDR tumors tested. Anal. of dEpoF, an analog possessing greater aq. soly. than dEpoB, showed curative effects similar to dEpoB against K562, CCRF-CEM, and MX-1 xenografts. These results indicate that dEpoB and dEpoF are efficacious antitumor agents with both a broad chemotherapeutic spectrum and wide safety margins.